Cyanate Ion and the Uremic Syndrome

J. D. Ingham

Propulsion Division

A critical survey is made of the literature that logically provides an hypothesis that relates the symptoms of kidney failure (uremic syndrome) to the presence of cyanate ion derived from metabolic urea. If the hypothesis can be unequivocally verified, the consequences will provide a solution to the problem of defining the primary toxic factor in uremia and should lead to substantial improvements in the available treatment for patients with kidney failure.

Introduction

The potential significance of cyanate ion with respect to the uremic syndrome was noted during some recent work on alternative methods of purification of uremic blood for application to treatment of kidney failure.

Metabolites, or waste products, that are eliminated by normal kidney function include urea, uric acid, indican, phenols, guanidine bases, organic acids, magnesium, phosphate, potassium, sulfate, and excess water. Although urea is formed in the largest quantity and its concentration in uremic blood is monitored to determine the requirements and effectiveness of conventional hemodialysis, it is not considered particularly toxic to persons with normal renal function. It is generally conceded that the toxic metabolites responsible for the pathological symptoms of uremia have not yet been determined. Thus, this absence of fundamental knowledge of the chemical and physiological processes attending renal failure remains as the greatest limitation in providing adequate and more effective treatment for uremic patients (Reference 1).

Discussion

Paradoxically, there is ample evidence in the medical literature that cyanate ion formed from metabolic urea can cause symptoms characteristic of uremia. However, it has not been proven nor stated elsewhere that cyanate accumulation and consequent carbamylation of proteins or

other physiological cyanate reactions are primarily responsible for the deterioration of uremic patients. In fact, the vast majority of publications on uremia or artificial kidney research do not mention cyanate at all, and there have been no published clinical methods developed to readily measure cyanate at expected physiological concentrations.

In 1953, Merrill, et al. (Reference 2), presented results to prove that urea was not the cause of uremic symptoms. They observed that patients improved clinically following hemodialysis even if their blood urea level did not decrease. Urea is sometimes given to patients as a diuretic or to relieve intercranial or intraocular pressure. In one hospital over 1300 nonuremic patients have tolerated a daily dose of 0.001 to 0.002 kg of urea/kg body weight for short periods without any ill effects (Reference 3).

Furthermore, up to 0.008 kg of urea/kg body weight has been given daily to normal dogs intravenously for seven days without manifestation of toxicity (Reference 4). However, uremic dogs expired within a few days when a 0.5 to 3 wt % aqueous urea solution was added to their peritoneal dialysis solution, while similar dogs dialyzed without added urea survived an average of 39 days (Reference 5). Gilboe and Javid (Reference 6) treated three groups of uremic dogs with normal peritoneal dialysis solution (Group I) and with dialysis solution containing 1 wt % aqueous urea solution (Group II) or 0.015 wt % potassium cyanate (Group III). Group I survived 14 $\pm$ 0.17[1] days, whereas Groups II and III survived 7 $\pm$ 0.60 and 6 $\pm$ 0.53 days, respectively. The same uremic symptoms, i.e., weakness, refusal to eat, diarrhea, intestinal hemorrhaging, and decreasing body temperature, were observed for Groups II and III. Since the concentration of cyanate in the tissue fluid of the Group III dogs was estimated to be approximately the same as that expected to be produced from a 1% aqueous urea solution in 24 hours, it can be concluded that it is probably the cyanate formed from urea, and not urea, that is primarily responsible for uremic symptoms. Other work has shown that the pharmacological effects of large doses of cyanate on healthy rats and rabbits are caused by cyanate and not any substance into which it may conceivably be transformed in the body [urea, ammonia, cyanide, or thiocyanate (Reference 7)].

At 38°C, about seven days are required to establish the equilibrium concentration of cyanate from urea, which is about 0.5% of the initial urea concentration (U), up to (U) $\cong$ 1 molar (Reference 8).

Therefore, nonuremics would not be expected to develop uremic symptoms from relatively large doses of urea because the urea and any

[1]Standard error.

urea products would be removed by normal kidney function before toxic amounts of cyanate would form.

It has been definitively established that cyanate reacts rapidly with sulfhydryl and amino groups of proteins and inhibits ribonuclease enzymatic activity *in vitro* (References 9 and 10). In fact, cyanate carbamylation and decarbamylation of functional groups have been used as a protecting reaction in the synthesis and study of biological compounds. Thus, it appears that the physiological activity of cyanate ion probably results from carbamylation of free sulfhydryl and amino groups in proteins or amino acids.

Summary and Conclusions

(1) In aqueous solutions of urea small equilibrium concentrations of cyanate are formed:

$$NH_2-\overset{\overset{O}{\|}}{C}-NH_2 \leftrightarrows NH_4^+ + CNO^- \qquad (I)$$

(2) In uremic patients cyanate ion is probably formed by Reaction I over a period of days, from the initial metabolic urea.

(3) Urea is not toxic to normal subjects, but 1% urea or 0.15% potassium cyanate added to the peritoneal dialysate of uremic dogs greatly accelerates the onset of uremic symptoms and death.

(4) It appears likely that uremic symptoms result from reaction of cyanate ion with sulfhydryl and amino groups in body proteins and amino acids:

$$RS^- + HNCO + HOH \leftrightarrows RS-\overset{\overset{O}{\|}}{C}-NH_2 + OH^- \qquad (II)$$

No further work has been done to clarify or define the role of cyanate ion in uremia.

One suggested reason for the apparent neglect in this area is the unavailability of a direct method for cyanate analysis at expected physiological concentrations. Therefore, Dr. J. D. Arterberry[2] is actively engaged in research on a new method of analysis for cyanate in blood and urine. Preliminary results with this method indicate the presence of expected concentrations of cyanate in normal urine samples. When the reliability of the method has been unequivocally established, uremic and normal blood will be analyzed for cyanate. Further, since Reaction

[2]USC School of Medicine and Chief of Staff, Central Receiving Hospital; also collaborator and consultant to JPL on the Laboratory's Purification of Uremic Blood task.

II is readily reversed at alkaline pH, the blood proteins of uremics can be decarbamylated to form cyanate to determine the extent of reaction of physiological cyanate compared with normal blood. If it is found that uremic proteins are partially carbamylated, the implications of Statement 4, above, will have been substantively verified. Experiments will then be carried out to determine methods of inhibition of carbamylation in uremic patients. If the role of cyanate ion in uremia is as significant as suggested here, the expected consequences of a continuation of this effort may be: (1) an elucidation of the primary causes of the uremic syndrome, and (2) much more efficient and acceptable methods of treatment of uremic patients.

Although any modifications of clinical treatment would be extremely presumptive until the proposed investigations are completed, the modifications might eventually involve occasional hemodialysis to remove excessive urea and other metabolites, and frequent oral or intravenous administration of relatively small amounts of nontoxic sulfhydryl compounds or other drugs. The latter would be developed to remove cyanate as it is formed, or to promote decarbamylation by shifting the equilibrium in Reaction II to the left.

References

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